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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/029,479	10/21/1998	SARA LAVI	2290.00061(T	6118

7590 04/09/2003

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/029,479	Lavi, S.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 16, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *45-48, 52-64, 67, and 77-91* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *80, 82, 83, and 85-91* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *45-48, 52-64, 67, 77-79, 81, and 84* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application is a 371 national stage filing of PCT/IB96/01021, filed August 30, 1996 which claims benefit to provisional application 60/003,114, filed September 1, 1995.

Applicants amendment filed January 16, 2003, paper number 25, has been received and entered. Claims 65, 68-76 have been canceled. Claims 77-91 have been added. Claims 45-48, 52-64, 67 and 77-91 are pending.

Election/Restriction

Claims 45-48, 52-64, 67 and 77-91 are pending. Claims 45-48, 53-64 and 67 have been withdrawn from consideration as being directed to a non-elected invention. It is noted that Applicants have elected the invention of group 5 drawn to treating cancer in a patient by administering a nucleic acid encoding PP2C alpha (see election filed October 23, 2000, paper number 11).

In addition, newly submitted claims 77-79, 81 and 84 are directed to an invention that is independent and distinct from the invention originally claimed for the following reasons: newly added claims 77-79 are drawn to a method of treating cancer by administering AAV or a portion thereof alone not requiring the administration of PP2C alpha encoding sequences (in light of the present disclosure AAV may reduce the endogenous expression of PP2C alpha by the cell); newly added claims 81 and 84 comprise a method wherein an antisence sequence is administered which may reduce any expression of PP2C alpha present.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 77-79, 81 and 84 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 80, 82, 83 and 85-91 are currently under examination as they are drawn to the elected invention of treating cancer in a patient by administering a nucleic acid encoding PP2C alpha.

This application contains claims drawn to an invention nonelected in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Newly added claims 80, 86-89 are objected to because of the following informalities:

Claim 82 is dependent on a non-elected claim. claim 82 should be rewritten as an independent claim encompassing all the limitations of the independent claim and any intervening claims. For the sake of compact prosecution, claim 82 will be interpreted to encompass all of the limitations set forth in the non-elected claims.

Claims 86-89 are recite and encompass non-elected subject matter as set forth in claims 77 and 84. Amending the claims to delete references to the non-elected claims would obviate the basis of this rejection.

Appropriate correction is required.

Specification

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). Specifically, on page 50, lines 35 and 36, two polynucleotide sequences are set forth, however neither are identified by SEQ ID NOs. 37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Information Disclosure Statement

It is noted that the specification contains a list of specific references (pages 62-69). The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for

consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80, 82, 83 and 85-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claim 80 is dependent on non-elected claim 77 and is being interpreted to encompass administering an AAV vector which comprises a nucleic acid sequences encoding PP2C alpha for treatment of any type of cancer. Newly added claims 82, 83 and 85 are drawn to treating specific types of cancer, colon cancer, invasive breast cancer, and liver cancer, respectively. Claims 86-88 provide more specific embodiments that the treated mammal is human, the PP2C alpha administered is human, and specific routes of administration. Claims 89-91 are drawn to further modifications to the vector wherein a targeting moiety is provided.

Initially, it is noted that the art teaches that various types of cancer do not show changes in PP2C alpha expression when tested (Kitamura *et al.*). Similarly, the present specification teaches that the expression of PP2C alpha is decreased in some of the tumor samples tested, however the specification teaches that samples from other tissues show no or a varying change of expression and location of the PP2C alpha in the cells tested (Example 4). Except in a statistically limited sample number, the present disclosure does not generally support a decrease in PP2C alpha expression to be associated with cancer any and all cancers, nor does it support that PP2C alpha is a direct cause or affect of the transformation process. As noted in the previous office actions, none of the working examples demonstrate that expression of PP2C

alpha can modulate the transformed phenotype of any human cancer or cancer cell line derived from a human. More importantly the data provided in the present disclosure derived from culturing transformed cell *in vitro* suggests that it is possibly the integration of the AAV, not PP2C alpha expression which is important for the transformed phenotype. It is noted that certain isolated cell lines which were infected with AAV demonstrate decreased PP2C alpha expression (and a reduced transformed phenotype), however, the specification teaches that in cells that have lost their transformed phenotype because of the integration of AAV. Significantly, contrary to ameliorating a transformed phenotype, the specification teaches that the transfection and expression of PP2C alpha restores the transformed phenotype and properties to these cells. The specification specifically teaches that PP2C alpha 'has a key role in the initiation and/or maintenance of transformed cells' (page 33; lines 18-20). Thus, contrary to any form of treatment, the only role for PP2C alpha in cells supported by the instant disclosure for the initiation and the maintenance of the transformed phenotype of cancer cells. Importantly, the evidence provided in the present disclosure indicates that the expression of PP2C alpha in any cell of a subject will only initiate and/or maintaining a transformed phenotype in the cells of a subject. The specification fails to provide a nexus between the transforming capability of PP2C alpha and affecting any form of treatment of any type of cancer by the expression of PP2C alpha.

Additionally, it is noted that claim 80 as interpreted to encompass the use of an AAV vector (non-elected claim 77) for the delivery and expression of PP2C alpha is in contradiction with the different roles that AAV and PP2C alpha expression may play in the phenotype of a cancer cell. Specifically, the specification teaches that administration of AAV will result in the

integration of AAV into the genome of the cell in the promoter region of PP2C alpha reducing the expression of PP2C alpha providing a reduced transformed phenotype, wherein administration of PP2C alpha to these same "untransformed" will result in the cell returning and/or obtaining a transformed phenotype. Though the specification provides literal support for using an AAV vector to express a PP2C alpha protein in general, the specification as a whole clearly teaches that AAV and PP2C alpha have opposing affects on a cell wherein the return of PP2C alpha provides a transformed phenotype. In this case generating a transformed cell would not be considered a method for treating cancer a mammal, rather it would be considered a method of generating cancer in a subject. Because providing AAV which expresses PP2C alpha would result in a transformed cell in a subject, the specification clearly does not enable the treatment of any form of cancer as encompassed by claim 80.

With respect to newly added claims 82, 83 and 85, as specifically drawn to the treatment of cancers of the colon, breast and liver it is noted that these claims rely *inter alia* on the observations that PP2C alpha expression is decreased in cancer cells. It is acknowledged that PP2C alpha gene expression appears to be decreased in certain types of cancer in the limited number of samples tested, however as argued above for the treatment of any cancer, the evidence provided in the instant specification, in particular the working examples in the present specification, it appears that the expression of PP2C ALPHA will only cause or enhance the transformed phenotype of the cancer cells in a subject. The guidance and the working evidence provided by the present specification is that PP2C alpha may play an role in the initiation and maintenance of a transformed phenotype, and that silencing elements present in AAV may

reduce a transformed phenotype in certain types of transformed cells. There is no guidance nor evidence that providing PP2C alpha to a transformed cell that demonstrates reduced PP2C alpha expression would result in an untransformed cell. The only role provided by the instant specification for PP2C alpha is for the initiation and maintenance of a transformed phenotype not treatment of cancer. Simply providing that evidence that certain cells exhibit decreased levels of expression of a particular gene does not provide a nexus for use of this gene in any particular methodology. In particular, with respect to the use of PP2C alpha, the only role associated with the expression of this gene is a transformed phenotype. The transformation process of a cell is a complex multi-step process, and given the limited evidence of expression of PP2C alpha in different types of cancer in light of its proposed role in the initiation of cancer indicates that the biology and role of PP2C in cancer is very complex and not completely understood. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. (see *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970)). In the instant case, the specification only teaches that providing PP2C alpha expression to a cell returns a cell to a transformed phenotype and causes cancer, therefore the specification fails to provide the necessary guidance for using PP2C alpha for treating any type of cancer.

With respect to gene therapy methodology in general, it is noted that the specification does discuss in general terms vectors which can be used in the claimed invention, and the examples provide more detailed guidance on the use of AAV as a possible vector. However, the experiments pointed to for support of an enabling disclosure are done *in vitro* with cell lines in

culture. Though working examples are not required to provide an enabling disclosure, because of the unpredictability of gene therapy protocols recognized in the art (as reviewed by Verma and Anderson) detailed guidance to the specific types of cells to be targeted for gene expression and a means to target said cells, guidance to the required levels of expression of the inserted gene and a means to obtain and control said levels of expression are required. As noted above, PP2C alpha has only been demonstrated to provide a transformed phenotype, and thus, the specification fails to fairly teach what a therapeutically effective amount of any vector would be since any expression would appear to initiate and maintain a transformed phenotype. Further, the instant specification provides a general review of many possible vectors, however fails to provide a nexus between a proposed role of PP2C alpha expression in transformed cells with the necessary guidance for the skilled artisan to alter said expression such that any treatment is achieved. There is no explicit teaching to which types of cancers are associated with decreased expression of PP2C alpha, and the specification is silent with respect to the necessary and detailed guidance on what receptors or ligand one should use to target a cancer cell. Importantly, the only specific guidance given for targeting a particular vector to a cell is the targeting of PP2C on the cell surface of a cell (page 24, lines 5-20). However, since the types of cancer which would be targeted for increasing the amounts of PP2C alpha expression in a cell would have decreased or no expression of PP2C alpha, this specific ligand would not serve a suitable targeting moiety in the instantly claimed methods. The Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated

> statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

(Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997)). The instant specification relies on the teachings of others for the delivery of a vector to cancer cells, however the specification fails to teach what specific cancer cells should be targeted, and if the art clearly teaches that these cells can in fact be targeted. As noted previously, the cited references and FDA approved protocol cited in Applicants previous arguments are not persuasive because they do not remedy the need for the specific guidance required to practice the instant invention. The protocols set forth in the cited references, represent different approaches for gene therapy but do not provide the necessary detailed guidance required to practice the specific methods as instantly claimed.

Applicants have proposed the expression of PP2C alpha for the treatment of cancer in a patient, however essentially all of the work required to ultimately develop therapeutic methods has been left for others. Altered expression of a polynucleotide encoding PP2C alpha may play a role in cancer, however the specification specifically teaches that the role of PP2C alpha is for the initiation and/or maintenance of a transformed phenotype, not any form of treatment At the time the claimed invention was

made, the instant specification does not provide the necessary teaching to provide a nexus between the proposed methods in the instant application and the art recognized problems associated with gene therapy. As discussed above and the previous office action, there are several art recognized limitations and unpredictability issues regarding gene therapy, that include: vector to be used for gene expression, production of effective concentration of the candidate polypeptide, delivery of the gene to the appropriated target cell, sustained expression and production of the candidate protein *in vivo*, and maintaining an effective level of the enzyme *in vivo*. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The present disclosure has not described nor provided examples of how the recited method of gene therapy differs from those presently found in the art, and in great part rely on the methods of gene delivery established by others, Applicants face the same shortcomings faced by others skilled in the art with regards to the specificity of cell targeting and the ability to regulate gene expression.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 80, 82, 83 and 85-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 80 is vague and unclear as interpreted to encompass the limitations of claim 77, in the recitation of 'a nucleic acid encoding a ΠΠ2X ΑΛΠΗΑ' because while the AAV vector is claimed to be used and administered to provide a therapeutic amount and affect there is no limitation or association with therapeutic amounts of ΠΠ2X ΑΛΠΗΑ. There is no limitation in claim 80 that ΠΠ2X ΑΛΠΗΑ even needs to be expressed. Amending claim 80 to be an independent claim, and more clearly indicating therapeutic amounts and affects of ΠΠ2X ΑΛΠΗΑ as drawn to the elected invention would obviate the basis of this rejection.

Claims 82, 83 and 85 are vague and unclear in the recitation of "effective to increase the level of PP2C α in the cytoplasm of the subject's cancerous' cells because there is insufficient antecedent basis for what is being measured in the cytoplasm. It is unclear if 'the level' of the vector, resulting RNA or resulting protein is being considered or measured, and what amount of any of these would be considered to achieve an "effective" amount of delivery. Dependent claims 86-91 are included in the rejection because they fail to further clarify the basis of the rejection.

Conclusion

No claim is allowed. As noted previously, the claims are free of the art of record because the art fails to teach a method of treating cancer in a mammal by gene therapy protocols in which the polynucleotide encoding phosphatase 2C alpha is expressed, however the claims are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630